CHAPTER 9

Bleeding and Bruising

Ivan Abdouch

Normal hemostasis is dependent on a complex and balanced process of clot formation and clot lysis. A number of congenital and acquired conditions can produce disruption of this process, resulting in spontaneous, excessive, or delayed bleeding and bruising.

Determining whether a pathologic or even clinically significant process is present can be obscured by the wide variation that exists among patients in their perceptions about bleeding or bruising. Because no standardized measure of bleeding severity exists, the clinician must rely on historical clues relative to the patient's bleeding history (e.g., bleeding after tooth extraction or other surgical procedures, menstrual history, anemia), dietary habits, and medication use.

ABNORMAL PLATELET FUNCTION

Abnormal platelet function can be caused by medications and/or disruption at any of the several levels of the normal process of primary hemostasis including: (1) endothelial injury; (2) platelet adhesion as platelets interact with von Willebrand factor (vWf) in the endothelium; (3) platelet aggregation, which is mediated by platelet glycoprotein IIb/IIIa; (4) platelet activation, which involves release of alpha and dense granules; the alpha granules contain hemostatic proteins like fibrinogen, and vWf, whereas the dense granules contain proaggregatory factors like adenosine diphosphate (ADP); and (5) formation of thromboxane A_2.

Signs

- Often present in early childhood with moderate to severe bruising or bleeding, usually recognized at the time of trauma or surgery but occasionally there is spontaneous bleeding
- Females may have menorrhagia that worsens with use of nonsteroidals.

Workup

- In vitro bleeding time
- Flow cytometry
- Platelet aggregation

HEMOPHILIA

Hemophilia is a congenital sex-linked recessive disorder occurring in approximately 1 in 10,000 births. Individuals with hemophilia have limited levels of specific clotting factors resulting in prolonged bleeding. The genetic transmission of hemophilia results in males with the disorder and females as carriers. The most common forms of hemophilia include factor VIII (most prevalent) and factor IX.

Symptoms

- Bleeding or bruising +++

Signs

- Family history of bleeding disorders particularly in the male members
- Prolonged bleeding
- Hemarthrosis, joint or muscle pain
- Swollen, warm, or stiff joints
- Multiple or large contusions
- Hematomas
- Trauma-induced or postoperative uncontrolled bleeding (including circumcision)
- Altered mental status post-head injury

Workup

- Screening tests
  - Bleeding time
  - Closure time
  - Platelet count
  - Activated partial thromboplastin time (aPTT)
- Studies to rule out other causes of bleeding such as:
  - Cancer
  - Liver disease
  - Bone marrow dysfunction
  - Medications
  - Immune system–related diseases
  - DIC (often associated with childbearing, cancer, or infection)
  - Eclampsia
  - Organ transplant rejection
  - Antibodies that destroy clotting factors
  - Exposure to snake venom
- Check factor VIII and IX specific assays if any abnormal screening test results (Table 9-1).
- aPTT—Elevated in moderate to severe hemophilia; may be normal in mild hemophilia (Table 9-2)
- Females—Check factor levels before any major surgery if:
  - Father, son, and/or brother have hemophilia (may have decreased factor levels)
  - Experience hemophilia-type symptoms (some women can be symptomatic carriers; severe menstrual bleeding is the most common symptom for women with lower factor levels)

Table 9-1. Differential Diagnoses Based on Findings

POSSIBLE CONDITION	PT	aPTT	BLEEDING TIME	PLATELET COUNT
Normal	+	+	+	+
vWf	+	+ or ⇑	+ or ⇑	+ or ⇓
Hemophilia A and B	+	⇑	+	+
Platelet defect	+	+	+ or ⇑	+ or ⇓

aPTT, Activated partial thromboplastin time; +, normal; ⇑, prolonged; *PT,* prothrombin; ⇓, reduced; *vWf,* von Willebrand factor.

Table 9-2. Categorization of Hemophilia by Factor Level

FACTOR LEVELS	SEVERITY OF DISEASE	COMPLICATIONS
>1 %	Severe	Spontaneous bleeds
1%-5%	Moderate	Occasional spontaneous bleeds; severe bleeds—surgery or trauma
5%-40%	Mild	Usually only bleeds with surgery or trauma

Comments and Treatment Considerations

Reduce complications by administering factor concentrate on arrival to the health care facility before any lab, intake paperwork, vitals, or ancillary services are obtained. Clotting factor replacement is very effective, but is extremely expensive; the financial stress on the family should be considered and addressed. Reaching an insurance lifetime maximum is common.

Desmopressin (DDAVP) can be used for non–life-threatening bleeds instead of factor concentrate for individuals with mild to moderate factor VIII deficiency and von Willebrand disease (Table 9-3). This medication can raise the factor two to eight times the baseline level.

Be aware of the possibility of the emergence of inhibitors—a severe complication for some individuals who use factor concentrate. This may be found when a person who normally responds to the factor concentrate continues to bleed. When this occurs the factor levels and the presence of inhibitors should be checked. A hematologist should be consulted and a second-line agent chosen.

Antifibrinolytic drugs can also be used for mouth bleeds. With all individuals with bleeding disorders, medicines that affect platelet function should not be used (e.g., aspirin and NSAIDs). Acetaminophen is a good alternative.

During testing and diagnosis, support the family by providing accurate information about the disease and educate them over

Table 9-3. Types of von Willebrand Disease

TYPE	CHARACTERISTIC	INHERITANCE	TREATMENT
1	vWf is reduced, usually do not bleed spontaneously, most common	Dominant: one parent	DDAVP by intravenous or intranasal Severe bleeds/ surgery may require factor VIII with vWf
2	vWf is abnormal (smaller and breaks down too easily or factor sticks to platelets too well)	Dominant: one parent	Factor VIII with vWf
3	Severe bleeding problems and has very low vWf and factor VIII	Recessive: both parents	Factor VIII with vWf
Pseudo	Similar to type 2 but the defects are in the platelets	Dominant: one parent	Platelet transfusion

DDAVP, Desmopressin; *vWf,* von Willebrand factor.

time. A follow-up visit should occur soon after the initial diagnosis to provide support, information, and a clarification for the families. Caregiving and coping with a chronic disease should be addressed with the family in each encounter. Because many individuals with hemophilia are treated at home, establishment of a collaborative and supportive relationship is imperative.

Due to the large volume of factor concentrates and other treatment modalities a hematologist should be part of the treatment team and should be consulted when a new diagnosis occurs and when significant injury or surgeries occur.

If the individual has a history of hemophilia and there is doubt about the possibility of a bleed occurring, err on the side of caution and treat. Because hemophilia is an uncommon disorder and families have knowledge of past treatment successes, the family should be encouraged to provide guidance to the treatment team.

Life-threatening bleeds include severe trauma, or trauma to the GI, CNS, neck, and throat. Serious bleeds involve joints, muscle, urinary tract, mouth, gums, and nose—these can cause serious secondary damage (e.g., arthritis, nerve damage, urinary tract damage). Joint bleeds are the most common complication in hemophilia.

Treatment options include:

- Daily prophylactic treatment for individuals with severe disease with frequent spontaneous bleeding (due to the difficulty with daily IV administration of factor, many young children will have a Port-A-Cath placed and parents will be trained to administer the factor at home)

- Periodic treatment when injury, surgery, or spontaneous bleed occurs
- Adjunctive therapy should be used in conjunction with factor replacement to aid in healing, decrease swelling, and aid in pain reduction.
  - RICE: Rest, Ice (20 minutes every 4 hours until swelling and pain decreases), Compression, and Elevation
  - May also need splinting, crutches, or wheelchair

MEDICATION-INDUCED

Acquired platelet dysfunction has been described as being second only to thrombocytopenia as the major cause of clinical bleeding disorders. The most common of drug induced bleeding disorders arise from the ingestion of aspirin and other NSAIDs that inhibit platelet production of thromboxane A_2. These drugs inhibit COX. The other agents are competitive and reversible inhibitors with more transient effects. Table 9-4 illustrates common drugs associated with platelet dysfunction.

Signs

- Clinical evidence of bleeding, but a normal platelet count and coagulation studies
- Easy bruising and bleeding confined to skin
- Occasionally patients will have prolonged oozing after surgery, particularly with procedures involving mucous membranes.

Workup

- Ask explicit questions to identify all prescribed drugs, over-the-counter medications, and any herbal preparations.
- Prolonged Ivy bleeding time; platelet aggregometry

Comments and Treatment Considerations

- Discontinue the culprit drug.
- Platelet transfusion in the setting of clinically significant bleeding
- Patients who have taken aspirin should be treated as if they have a mild hemostatic defect for the next 5 to 7 days.

VON WILLEBRAND'S DISORDER

von Willebrand's disease (vWD) is an autosomal disorder with three specific types. Type 1 is an autosomal dominant disorder and types 2 and 3 are recessive disorders. vWD is the most common form of bleeding disorders, with a prevalence of approximately 1% to 2% of the population. vWf works in conjunction with platelets to stick to the damaged part of the body. It is also used to transport factor VIII to the site of the injury. Individuals with vWD have problems with one or both of these issues.

Table 9-4. Common Drugs Causing Platelet Dysfunction

INTERFERES WITH PLATELET MEMBRANE	INHIBITION OF PROSTAGLANDIN SYNTHESIS	INHIBITION OF PLATELET PHOSPHODIESTERASE	UNKNOWN MECHANISM OF ACTION
Amitriptyline	Aspirin	Caffeine	Acetazolamide
Imipramine	NSAIDs	Dipyridamole	Ethacrynic acid
Chlorpromazine	Furosemide	Aminophylline	Hydroxychloroquine
Cocaine	Verapamil	Theophylline	Nitroprusside
Lidocaine	Hydralazine	Vinblastine	Cyproheptadine
Isoproterenol	Cyclosporine A	Vincristine	Nitroglycerin
Propranolol	Hydrocortisone	Colchicine	Famotidine
Penicillin		Papaverine	Cimetidine
Ampicillin		Clopidogrel	
Cephalothin		Ticlopidine	
Promethazine			
Diphenhydramine			
Carbenicillin			

Signs

- Family history of bleeding disorders
- Prolonged bleeding
- Hemarthrosis
- Joint or muscle pain
- Swollen, warm, or stiff joints
- Multiple or large contusions
- Hematomas
- Trauma-induced or postoperative uncontrolled bleeding (including circumcision)
- Altered mental status post-head injury
- Abnormal menstrual bleeding

Workup

- Screening tests
  - Bleeding time
  - Closure time
  - Platelet count
  - aPTT
- If results are abnormal, vWf and factor VIII specific assay tests should be conducted (see Table 9-1).
- Studies to rule out other causes of bleeding such as cancer, liver disease, bone marrow dysfunction, medications, immune system–related diseases, DIC (often associated with childbearing, cancer, or infection), eclampsia, organ transplant rejection, antibodies that destroy clotting factors, and exposure to snake venom
- Check vWf assay if any abnormal screening test results (see Table 9-1).

Comments and Treatment Considerations

Reduce complications by administering factor concentrate on arrival to the health care facility before any lab, intake paperwork, vitals or ancillary services are obtained. Clotting factor replacement is very effective, but is extremely expensive; the financial stress on the family should be considered and addressed. Reaching an insurance lifetime maximum is common.

DDAVP can be used for non–life-threatening bleeds instead of factor concentrate for individuals with mild to moderate factor VIII deficiency and vWD. This medication can raise factor two to eight times the baseline level.

Be aware of the possibility of the emergence of inhibitors—a severe complication for some individuals who use factor concentrate. This may be found when a person who normally responds to the factor concentrate continues to bleed. When this occurs the factor levels and the presence of inhibitors should be checked. A hematologist should be consulted and a second-line agent chosen.

Antifibrinolytic drugs can also be used for mouth bleeds. With all individuals with bleeding disorders, medicines that affect platelet function should not be used (e.g., aspirin and NSAIDs). Acetaminophen is a good alternative.

During the testing and diagnosis, support the family by providing accurate information about the disease, and educate them over time. A follow-up visit should occur soon after the initial diagnosis to provide support, information and a clarification for the families. Caregiving and coping with a chronic disease should be addressed with the family in each encounter. Because many individuals with hemophilia are treated at home, establishment of a collaborative and supportive relationship is imperative.

Due to the large volume of factor concentrates and other treatment modalities a hematologist should be part of the treatment team and should be consulted when a new diagnosis occurs and when significant injury or surgeries occur.

Disease should be categorized so that treatment can be specific to disease type (see Table 9-3).

THROMBOCYTOPENIA

Symptoms

- Bleeding or bruising +++

Signs

- Platelet count less than 150,000 ++++
- Less than 50,000: petechiae appear +++
- Less than 20,000: bleeding from gums, nose, GI tract, or brain may occur ++
- Splenomegaly and systemic symptoms (e.g., fever) suggest that thrombocytopenia is secondary to another condition.
- Hemarthrosis occurs with coagulation disorders but not with platelet dysfunction.

Workup

- May be due to medications, decreased platelet production, increased destruction, or sequestration.
- Medication history—explicit questions to identify all prescribed drugs, over-the-counter medications, and any herbal preparations; medication-induced thrombocytopenia is often am empirical diagnosis, supported only by resolution of thrombocytopenia after discontinuation of therapy with the suspected drug (Table 9-5).
- CBC and platelet count
- Bone marrow analysis if needed (decreased megakaryocytes signal decreased platelet production; increased megakaryocytes signal increased platelet destruction)
- Other studies as dictated by specific circumstances as outlined in the following text. May need radiologic confirmation of splenomegaly.

Comments and Treatment Considerations

Treat the underlying disorder if feasible. In the case of medications, remove the offending agent and maintain symptomatic treatment of the patient (give oral prednisone 1 mg/kg once daily if platelet count $<10{,}000/mm^3$); platelet counts should recover within 5 to 7 days.

Table 9-5. Drugs Associated with Thrombocytopenia, with Level I Evidence (Definite) or Level II Evidence (Probable)

Abciximab	Clozapine	Gold salts	Olanzapine	Simvastatin
Acetaminophen	Cyclosporine	Haloperidol	Ondansetron	Sulfadiazine
Acetazolamide	Desmopressin	Hydantoin	Penicillin	Sulfathiozole
Acyclovir	Diazepam	HCTZ	Phenytoin	Suramin
Ampicillin	Diazoxide	Hydroxyurea	Piroxicam	Teicoplanin
Atorvastatin	Diclofenac	Hepatitis B vaccine/interferon	Plicamycin	Terbinafine
Benztropine	Diltiazem	Levamisole	Prednisone	Ticlopidine
Bleomycin	Doxepin	L-Tryptophan	Procainamide	Trimethoprim
Carbamazepine	Enalapril	Measles vaccine	Prochlorperazine	Valproate
Cephalosporins	Famotidine	Mesalamine	Pyrimethamine	Vancomycin
Chlorpromazine	Fluphenazine	Methylphenidate	Quinidine	
Cimetidine	Furosemide	Moxalactam	Ranitidine	
Ciprofloxacin	Ganciclovir	Naproxen	Rifampin	
Clopidogrel	Gentamicin	Octreotide	Rituximab	

If major bleeding is present, platelet transfusions, IVIg, and high doses of parenteral glucocorticoids (comparable to treatment of idiopathic thrombocytopenia [ITP]) are appropriate.

Medication-induced thrombocytopenia typically presents as isolated thrombocytopenia in a patient who is taking several medications. The main issue is to distinguish between drug-induced thrombocytopenia and ITP. Medications begun within the last month are more likely the cause of thrombocytopenia than are medications taken regularly for many years. Mechanisms include hapten-type immune reaction, innocent bystander–type immune reaction, direct toxicity, and heparin-induced reaction.

Direct Toxicity

- Causes suppressed thrombopoiesis
- Cancer chemotherapy agents, pesticides, and organic solvents have been implicated in this type of thrombocytopenia.

HAPTEN-TYPE IMMUNE REACTIONS

Symptoms

- Most common type of thrombocytopenia
- Usually appears at least 7 days after the start of a new medication
- Can occur sooner in cases of reexposure to a drug that was previously taken

HEPARIN-INDUCED THROMBOCYTOPENIA I (HIT I)

- Occurs within the first 2 days after heparin initiation
- Often returns to normal with continued heparin administration
- More common than HIT II
- Is of no clinical consequence

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT II)

HIT II, the more serious form, is an immune-mediated disorder characterized by the formation of antibodies against the heparin-platelet factor IV complex.

Symptoms

- Bleeding and bruising +++

Signs

Early:

- Increased bruising +
- Petechiae +

- Ecchymoses +
- Epistaxis +
- Necrotic skin lesions +

Later:
- Bleeding ++
- Severe purpura
- Platelet count that has fallen 50% or more from a prior value +
- Heparin therapy within the preceding 5 to 10 days, or in a patient receiving prolonged treatment with LMWH
- Thrombosis associated with thrombocytopenia +++

Workup
- Diagnosis of HIT is made on clinical grounds; assays with the highest sensitivity and specificity may not be readily available and have a slow turnaround time.
- Most specific diagnostic tests: Serotonin release assays, heparin-induced platelet aggregation assays, and solid phase immunoassays.
- Patients with HIT II also have elevated platelet-associated IgG levels, but this is a nonspecific finding.
- 14C-Serotonin release assay: Gold standard among the diagnostic tests for HIT II
- Heparin-induced platelet aggregation: More than 90% specific, but lacks sensitivity.
- Solid phase enzyme-linked immunosorbent assay (ELISA) immunoassay: Best used along with one of the functional assays rather than as a single test

Comments and Treatment Considerations
Immediately stop exposure to heparin, including heparin-bonded catheters and heparin flushes. Avoid LMWH.
- Lepirudin (Refludan): Recombinant hirudin, FDA-approved treatment of HIT complicated by thrombosis.
  - Initial dose of 0.4 mg/kg (up to 44 mg) IV bolus followed by an infusion of 0.15 mg/kg/hr (up to 16.5 mg/hr) for 2 to 10 days
  - Adjust infusion rate according to aPTT ratio
- Warfarin: Initiate while the patient has been stably anticoagulated with a thrombin-specific inhibitor, and when the platelet count has increased to 100,000/μL or higher. The use of warfarin in the absence of other anticoagulants should be avoided. Dose is patient specific.
- Bivalirudin: Hemodialyzable direct thrombin inhibitor and hirudin analog; FDA approved for patients with or at risk of HIT who are undergoing percutaneous coronary intervention.
- Argatroban: Another direct thrombin inhibitor; monitor its effect with aPTT
  - In patients with normal hepatic function, the starting dose is 2 mcg/kg/min by continuous IV infusion.
  - Adjust rate to maintain the aPTT at 1.5 to 3 times baseline

Decreased platelet production can be due to:
- Infections (including HIV)
- Chemotherapy or radiation therapy
- Deficiency of folate or vitamin B_{12} (especially seen with ethanol abuse)
- Marrow infiltration by tumor or storage diseases
- Marrow failure due to aplastic anemia
- Leukemia
- Myelodysplastic syndrome

INCREASED PLATELET DESTRUCTION

Alloimmune Thrombocytopenia
- Posttransfusion purpura: Up to 3% of the population is homozygous human platelet antigen (HPA)-1b due to amino acid substitution in the platelet glycoprotein IIb/IIIa antigen. When exposed to blood products from a person who is HPA-1a, antibodies develop that become clinically apparent 10 days posttransfusion. The resulting thrombocytopenia may last for weeks but will respond to IVIg.
- Neonatal alloimmune thrombocytopenia: Occurs in 1/200 pregnancies but is clinically significant in 1/1500. Most cases involve a mother who is HPA-1b and a baby who is HPA-1a. Thrombocytopenia occurs during the first pregnancy in half of cases.

Immune Thrombocytopenic Purpura
- Variety of immune conditions that result in problems with primary hemostasis (formation of the initial hemostatic plug)
  - Acute ITP: Self-limited form that usually occurs after a viral illness. Predominantly in children with peak age from 3 to 5 years. Incidence 5/100,000.
  - Chronic ITP: Platelet count low for more than 6 months. Peak age 20 to 40 years old. More common in females (1.7:1). Incidence 3 to 5/100,000.
  - Secondary ITP: Can occur with systemic lupus erythematosus, antiphospholipid antibody syndrome, IgA deficiency, hepatitis C, lymphomas and chronic lymphocytic leukemia, HIV, heparin, and quinidine.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Thrombocytopenic purpura is characterized by the presence of increased vWf precursors in the endothelial cells due to abnormal function of the enzyme ADAMTS13. Ultralarge multimers induce platelet aggregation, resulting in platelet consumption and occlusion of the small blood vessels. They are especially dangerous in brain and kidney.
- Sporadic form: Due to antibodies or toxins that inhibit ADAMTS13. These include cancer, chemotherapy, medications such as ticlopidine, cyclosporine A, tacrolimus, and quinine. Presents with

petechiae and neurologic symptoms ranging from headache and confusion to seizures and coma. May occur about 3 weeks after a flulike illness.
- Chronic, recurrent form (childhood thrombotic thrombocytopenic purpura [TTP]): Probably due to congenital deficiency of ADAMTS13. May be treated with transfusions of platelet-poor fresh-frozen plasma every 3 weeks.

Innocent Bystander–Type Immune Reaction
- Most often associated with quinidine

Sequestration of Platelets
- Platelets are sequestered in spleen or liver due to liver disease or malignancy.
- Presents with mild to moderate thrombocytopenia
- Presents with mild decrease in neutrophils and hemoglobin in the peripheral blood
- Presents with normal bone marrow
- May need radiologic confirmation of splenomegaly

THROMBOCYTOSIS

The most common condition is essential thrombocythemia—a myeloproliferative disorder (along with polycythemia vera and idiopathic myelofibrosis). Consider this diagnosis if there are no other causes of increased platelets such as arthritis, iron deficiency anemia, splenectomy, or chronic myelogenous leukemia.

Signs
- Mildly enlarged spleen
- Abnormal clotting in the brain or heart can be deadly.
- In pregnancy, fetal growth restriction, spontaneous abortion, and placental abruption

Workup
- Platelet count greater than 600,000; may be as high as 2 million
- Increased megakaryocytes in the bone marrow
- Abnormal clonal stem cell

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